CLAIMS

1. A crystal of a pharmaceutically acceptable salt of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea.

2. The crystal according to claim 1, which is suitable for an oral pharmaceutical preparation.

3. The crystal according to claim 1 or 2, wherein said salt is an inorganic acid salt or an organic acid salt.

4. The crystal according to claim 1 or 2, wherein said salt is selected from the group consisting of hydrochlorides, nitrates, sulfates, methanesulfonates, p-toluenesulfonates, and maleates.

5. The crystal according to claim 1 or 2, which is selected from the group consisting of form I crystal of hydrochloride, form II crystal of hydrochloride, form I crystal of p-toluenesulfonate, form II crystal of p-toluenesulfonate, and form II crystal of maleates of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea.

6. The crystal according to claim 1 or 2, wherein said salt is a hydrochloride.

7. The crystal according to claim 6, wherein said hydrochloride is a hydrochloride monoadduct.

8. The crystal according to claim 6 or 7, wherein said hydrochloride is a solvent adduct.

9. The crystal according to claim 8, wherein said solvent is water.

10. The crystal according to claim 6 or 7, which is a water monoadduct.

11. The crystal according to claim 6, wherein said hydrochloride is a hydrochloric acid monoadduct and a monohydrate.

12. The crystal according to claim 1 or 2, which is form I crystal of hydrochloride of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea.

13. The crystal according to claim 1 or 2, wherein said salt is a hydrochloric acid monoadduct and a monohydrate, and

in powder X-ray diffractometry, has peaks with not less than 10% relative intensity at at least the following diffraction angles (2θ):

Table A-1

Diffraction angle (2θ)
11.47 ± X
22.59 ± X
23.02 ± X
26.27 ± X
26.63 ± X

wherein X is 0 to 0.20.

14. The crystal according to claim 13, wherein the relative intensity in said diffraction angles (2θ) is not less than 15%.

15. The crystal according to claim 13, wherein the relative intensity in said diffraction angles (2θ) is not less than 20%.

16. The crystal according to claim 13, wherein the

relative intensity in said diffraction angles (2θ) is not less than 25%.

17. The crystal according to claim 13, wherein the relative intensity in said diffraction angles (2θ) is not less than 30%.

18. The crystal according to any one of claims 13 to 17, wherein X is 0 to 0.10.

19. The crystal according to claim 1 or 2, wherein said salt is a hydrochloric acid monoadduct and a monohydrate, and

in powder X-ray diffractometry, has peaks with not less than 10% relative intensity at at least the following diffraction angles (2θ):

Table B-1

Diffraction angle (2θ)
8.76 ± X
11.47 ± X
15.28 ± X
17.16 ± X
17.53 ± X
18.80 ± X
20.02 ± X
22.59 ± X
23.02 ± X
25.32 ± X
25.43 ± X
26.27 ± X
26.63 ± X
27.00 ± X
28.57 ± X

wherein X is 0 to 0.20.

20. The crystal according to claim 19, wherein the relative intensity in said diffraction angles (2θ) is not less than

15%.

21. The crystal according to claim 19, wherein the relative intensity in said diffraction angles (2θ) is not less than 20%.

22. The crystal according to any one of claims 19 to 21, wherein X is 0 to 0.10.

23. The crystal according to claim 1 or 2, wherein said salt is a hydrochloric acid monoadduct and a monohydrate, and

in powder X-ray diffractometry, has the following diffraction angles (2θ) and relative intensities:

Table 1

Diffraction angle (2θ)	Relative intensity
8.76	22
11.47	100
15.28	21
17.16	21
17.53	23
18.80	21
20.02	25
22.59	35
23.02	37
25.32	29
25.43	23
26.27	36
26.63	32
27.00	29
28.57	28

24. The crystal according to claim 1 or 2, wherein said salt is a hydrochloric acid monoadduct, and

in powder X-ray diffractometry, has peaks with not less than 10% relative intensity at at least the following diffraction angles (2θ):

Table A-2

Diffraction angle (2θ)
12.15 ± X
12.54 ± X
21.32 ± X
21.48 ± X
22.13 ± X
24.12 ± X
25.22 ± X
25.95 ± X

wherein X is 0 to 0.20.

25. The crystal according to claim 24, wherein the relative intensity in said diffraction angles (2θ) is not less than 15%.

26. The crystal according to claim 24, wherein the relative intensity in said diffraction angles (2θ) is not less than 20%.

27. The crystal according to claim 24, wherein the relative intensity in said diffraction angles (2θ) is not less than 25%.

28. The crystal according to claim 24, wherein the relative intensity in said diffraction angles (2θ) is not less than 30%.

29. The crystal according to any one of claims 24 to 28, wherein X is 0 to 0.10.

30. The crystal according to claim 1 or 2, wherein said salt is a hydrochloric acid monoadduct, and

in powder X-ray diffractometry, has peaks with not less than 10% relative intensity at at least the following diffraction angles (2θ):

Table B-2

Diffraction angle (2θ)
9.37 ± X
12.15 ± X
12.54 ± X
12.88 ± X
21.32 ± X
21.48 ± X
21.82 ± X
22.13 ± X
23.16 ± X
24.12 ± X
25.22 ± X
25.95 ± X

wherein X is 0 to 0.20.

31. The crystal according to claim 30, wherein the relative intensity in said diffraction angles (2θ) is not less than 15%.

32. The crystal according to claim 30, wherein the relative intensity in said diffraction angles (2θ) is not less than 20%.

33. The crystal according to any one of claims 30 to 32, wherein X is 0 to 0.10.

34. The crystal according to claim 1 or 2, wherein said salt is a hydrochloric acid monoadduct, and

in powder X-ray diffractometry, has the following diffraction angles (2θ) and relative intensities:

Table 2

Diffraction angle (2θ)	Relative intensity
9.37	26
12.15	37
12.54	32

12.88	29
21.32	31
21.48	30
21.82	27
22.13	37
23.16	23
24.12	37
25.22	100
25.95	31

35. The crystal according to claim 1 or 2, wherein said salt is a p-toluenesulfonate monoadduct and a monohydrate, and

in powder X-ray diffractometry, has peaks with not less than 30% relative intensity at at least the following diffraction angles (2θ):

Table A-3

Diffraction angle (2θ)
4.92 ± X
9.48 ± X
16.17 ± X
16.85 ± X
19.03 ± X
24.36 ± X
25.27 ± X
26.88 ± X

wherein X is 0 to 0.20.

36. The crystal according to claim 35, wherein the relative intensity in said diffraction angles (2θ) is not less than 40%.

37. The crystal according to claim 35, wherein the relative intensity in said diffraction angles (2θ) is not less than 50%.

38. The crystal according to any one of claims 35 to 37,

wherein X is 0 to 0.10.

39. The crystal according to claim 1 or 2, wherein said salt is a p-toluenesulfonate monoadduct and a monohydrate, and

in powder X-ray diffractometry, has peaks with not less than 10% relative intensity at at least the following diffraction angles (2θ):

Table B-3

Diffraction angle (2θ)
4.92 ± X
9.48 ± X
15.74 ± X
16.17 ± X
16.85 ± X
17.19 ± X
17.55 ± X
19.03 ± X
21.19 ± X
21.36 ± X
21.80 ± X
22.30 ± X
23.75 ± X
23.93 ± X
24.36 ± X
25.27 ± X
25.78 ± X
26.88 ± X
28.15 ± X
28.41 ± X

wherein X is 0 to 0.20.

40. The crystal according to claim 39, wherein the relative intensity in said diffraction angles (2θ) is not less than 20%.

41. The crystal according to claim 39 or 40, wherein X is 0 to 0.10.

42. The crystal according to claim 1 or 2, wherein said salt is a p-toluenesulfonate monoadduct and a monohydrate, and

in powder X-ray diffractometry, has the following diffraction angles (2θ) and relative intensities:

Table 13

Diffraction angle (2θ)	Relative intensity
4.92	77
9.48	65
15.74	36
16.17	82
16.85	68
17.19	30
17.55	45
19.03	100
21.19	49
21.36	44
21.80	46
22.30	26
23.75	33
23.93	38
24.36	56
25.27	76
25.78	43
26.88	83
28.15	29
28.41	41

43. The crystal according to claim 1 or 2, wherein said salt is a p-toluenesulfonate monoadduct and a monohydrate, and

in powder X-ray diffractometry, has peaks with not less than 30% relative intensity at at least the following diffraction

angles (2θ):

Table A-4

Diffraction angle (2θ)
4.86 ± X
9.42 ± X
18.93 ± X
21.17 ± X
24.03 ± X
25.57 ± X
27.16 ± X
28.48 ± X

wherein X is 0 to 0.20.

44. The crystal according to claim 43, wherein the relative intensity in said diffraction angles (2θ) is not less than 40%.

45. The crystal according to claim 43, wherein the relative intensity in said diffraction angles (2θ) is not less than 50%.

46. The crystal according to any one of claims 43 to 45, wherein X is 0 to 0.10.

47. The crystal according to claim 1 or 2, wherein said salt is a p-toluenesulfonate monoadduct and a monohydrate, and

in powder X-ray diffractometry, has peaks with not less than 10% relative intensity at at least the following diffraction angles (2θ):

Table B-4

Diffraction angle (2θ)
4.86 ± X
9.42 ± X
12.45 ± X
15.83 ± X

16.16 ± X
16.74 ± X
17.31 ± X
17.62 ± X
18.93 ± X
21.17 ± X
21.82 ± X
22.39 ± X
24.03 ± X
24.31 ± X
25.57 ± X
26.01 ± X
27.16 ± X
28.48 ± X

wherein X is 0 to 0.20.

48. The crystal according to claim 47, wherein the relative intensity in said diffraction angles (2θ) is not less than 20%.

49. The crystal according to claim 47 or 48 wherein X is 0 to 0.10.

50. The crystal according to claim 1 or 2, wherein said salt is a p-toluenesulfonate monoadduct and a monohydrate, and

in powder X-ray diffractometry, has the following diffraction angles (2θ) and relative intensities:

Table 14

Diffraction angle (2θ)	Relative intensity
4.86	82
9.42	54
12.45	28
15.83	44
16.16	37
16.74	39

17.31	38
17.62	42
18.93	67
21.17	51
21.82	25
22.39	26
24.03	50
24.31	39
25.57	82
26.01	35
27.16	100
28.48	50

51. A process for producing form I crystal of hydrochloride of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea, said process comprising the steps of:

adding hydrochloric acid and ethanol to a solution of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea in an aprotic polar solvent; and precipitating crystals from the solution.

52. The process according to claim 51, wherein, in addition to hydrochloric acid and ethanol, water is further added.

53. The process according to claim 51 or 52, wherein said aprotic polar solvent is N,N-dimethylformamide or N,N-dimethylacetamide.

54. The process according to any one of claims 51 to 53, wherein said hydrochloric acid has a concentration of 10 to 14 N.

55. The process according to any one of claims 51 to 54, wherein said crystal is one according to any one of claims 13 to

23.

56. A process for producing form II crystal of hydrochloride of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea, said process comprising the steps of:

adding hydrochloric acid and 1-propanol to a solution of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea in an aprotic polar solvent; and precipitating crystals from the solution.

57. The process according to claim 56, wherein said aprotic polar solvent is N,N-dimethylformamide or N,N-dimethylacetamide.

58. The process according to claim 56 or 57, wherein said hydrochloric acid has a concentration of 10 to 14 N.

59. The process according to any one of claims 56 to 58, wherein said crystal is one according to any one of claims 24 to 34.

60. A process for producing form I crystal of a p-toluenesulfonate of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea, said process comprising the steps of:

adding p-toluenesulfonic acid to a solution of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea in acetonitrile and precipitating crystals from the solution; and

dissolving said crystals in methanol and water to prepare a solution and precipitating crystals from the solution.

61. The process according to claim 60, wherein said crystal is one according to any one of claims 35 to 42.

62. A process for producing form II crystal of a p-toluenesulfonate of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea, said process comprising the steps of:

adding p-toluenesulfonic acid to a solution of N-{2-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-3-isoxazolyl)urea in acetonitrile and precipitating crystals from the solution; and

dissolving said crystals in N,N-dimethylformamide to prepare a solution, adding water to the solution, and precipitating crystals from the solution.

63. The process according to claim 60, wherein said crystal is one according to any one of claims 43 to 50.

64. A phermaceutical composition comprising the crystal according to any one of claims 1 to 50 and a pharmaceutically acceptable carrier.

65. The pharmaceutical composition according to claim 64, for use in the therapy of a disease selected from the group consisting of tumors, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, Kaposi's sarcoma, and exudation type age-related maculopathy.

66. The pharmaceutical composition according to claim 64, for use in the prophylaxis of metastasis or therapy of solid tumors.

67. The pharmaceutical composition according to any one of claims 64 to 66, which is administered orally.

68. A method for the therapy of a disease selected from the group consisting of tumors, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, Kaposi's sarcoma, and exudation type age-related maculopathy, comprising the step of

administering an effective amount of the crystal according to any one of claims 1 to 50 to a mammal patient.

69. A method for the prophylaxis of metastasis or therapy of a solid tumor, comprising the step of administering an effective amount of the crystal according to any one of claims 1 to 50 to a mammal patient.

70. The method according to claim 68 or 69, wherein said administration is oral administration.

71. A method for inhibiting angiogenesis of a target blood vessel, comprising the step of bringing an effective amount of the crystal according to any one of claims 1 to 50 into contact with vascular endothelial cells of said target blood vessel.

72. Use of the crystal according to any one of claims 1 to 50, for the manufacture of a pharmaceutical for use in the therapy of a disease selected from the group consisting of tumors, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, Kaposi's sarcoma, and exudation type age-related maculopathy.

73. Use of the crystal according to any one of claims 1 to 50, for the manufacture of a pharmaceutical for use in the prophylaxis of metastasis or therapy of solid tumors.